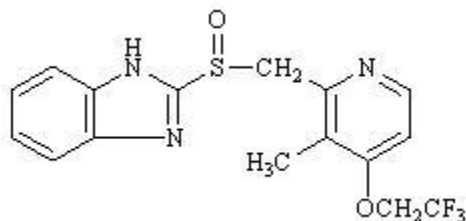


LANSOPRAZOLE DR - lansoprazole capsule, delayed release

Stat Rx USA

11 DESCRIPTION

The active ingredient in Lansoprazole Delayed-Release Capsules is lansoprazole, a substituted benzimidazole, 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl] methyl] sulfinyl] benzimidazole, a compound that inhibits gastric acid secretion. Its empirical formula is $C_{16}H_{14}F_3N_3O_2S$ with a molecular weight of 369.37. Lansoprazole has the following structure:



Lansoprazole is a white to brownish-white odorless crystalline powder which melts with decomposition at approximately 166°C.

Lansoprazole is freely soluble in dimethylformamide; soluble in methanol; sparingly soluble in ethanol; slightly soluble in ethyl acetate, dichloromethane and acetonitrile; very slightly soluble in ether; and practically insoluble in hexane and water.

Lansoprazole is stable when exposed to light for up to two months. The rate of degradation of the compound in aqueous solution increases with decreasing pH. The degradation half-life of the drug substance in aqueous solution at 25°C is approximately 0.5 hour at pH 5.0 and approximately 18 hours at pH 7.0.

Lansoprazole is supplied in delayed-release capsules for oral administration.

Lansoprazole delayed-release capsules are available in two dosage strengths: 15 mg and 30 mg of lansoprazole per capsule. Each delayed-release capsule contains enteric-coated granules consisting of 15 mg or 30 mg of lansoprazole (active ingredient) and the following inactive ingredients: sugar sphere, sucrose, methacrylic acid copolymer, low substituted hydroxypropyl cellulose, starch, magnesium carbonate, talc, polyethylene glycol, titanium dioxide, polysorbate 80, hydroxypropyl cellulose, colloidal silicon dioxide, D and C Red No. 28, FD and C Blue No. 1, FD and C Green No. 3, and FD and C Red No. 40.

12 CLINICAL PHARMACOLOGY 12.1 Mechanism of Action

Lansoprazole belongs to a class of antisecretory compounds, the substituted benzimidazoles, that suppress gastric acid secretion by specific inhibition of the (H^+, K^+) -ATPase enzyme system at the secretory surface of the gastric parietal cell. Because this enzyme system is regarded as the acid (proton) pump within the parietal cell, lansoprazole has been characterized as a gastric acid-pump inhibitor, in that it blocks the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated gastric acid secretion irrespective of the stimulus. Lansoprazole does not exhibit anticholinergic or histamine type-2 antagonist activity.

12.2 Pharmacodynamics

Antisecretory Activity: After oral administration, lansoprazole was shown to significantly decrease the basal acid output and significantly increase the mean gastric pH and percent of time the gastric pH was greater than 3 and greater than 4. Lansoprazole also significantly reduced meal-stimulated gastric acid output and secretion volume, as well as pentagastrin-stimulated acid output. In patients with hypersecretion of acid, lansoprazole significantly reduced basal and pentagastrin-stimulated gastric acid secretion. Lansoprazole inhibited the normal increases in secretion volume, acidity and acid output induced by insulin.

After the initial dose in this study, increased gastric pH was seen within 1 to 2 hours with 30 mg of lansoprazole and 2 to 3 hours with 15 mg of lansoprazole. After multiple daily dosing, increased gastric pH was seen within the first hour post-dosing with 30 mg of lansoprazole and within 1 to 2 hours post-dosing with 15 mg of lansoprazole.

Acid suppression may enhance the effect of antimicrobials in eradicating *Helicobacter pylori* (*H. pylori*). The percentage of time gastric pH was elevated above 5 and 6 was evaluated in a crossover study of lansoprazole given daily, twice daily and three times daily.

The inhibition of gastric acid secretion as measured by intragastric pH gradually returned to normal over two to four days after multiple doses. There was no indication of rebound gastric acidity.

Enterochromaffin-like (ECL) Cell Effects

During lifetime exposure of rats with up to 150 mg/kg/day of lansoprazole dosed seven days per week, marked hypergastrinemia was observed followed by ECL cell proliferation and formation of carcinoid tumors, especially in female rats. Gastric biopsy specimens from the body of the stomach from approximately 150 patients treated continuously with lansoprazole for at least one year did not show evidence of ECL cell effects similar to those seen in rat studies. Longer term data are needed to rule out the possibility of an increased risk of the development of gastric tumors in patients receiving long-term therapy with lansoprazole. [See *Nonclinical Toxicology* (13.1)]

Other Gastric Effects in Humans

Lansoprazole did not significantly affect mucosal blood flow in the fundus of the stomach. Due to the normal physiologic effect caused by the inhibition of gastric acid secretion, a decrease of about 17% in blood flow in the antrum, pylorus, and duodenal bulb was seen. Lansoprazole significantly slowed the gastric emptying of digestible solids. Lansoprazole increased serum pepsinogen

levels and decreased pepsin activity under basal conditions and in response to meal stimulation or insulin injection. As with other agents that elevate intragastric pH, increases in gastric pH were associated with increases in nitrate-reducing bacteria and elevation of nitrite concentration in gastric juice in patients with gastric ulcer. No significant increase in nitrosamine concentrations was observed.

Serum Gastrin Effects

In over 2100 patients, median fasting serum gastrin levels increased 50% to 100% from baseline but remained within normal range after treatment with 15 to 60 mg of oral lansoprazole. These elevations reached a plateau within two months of therapy and returned to pretreatment levels within four weeks after discontinuation of therapy.

Endocrine Effects

Human studies for up to one year have not detected any clinically significant effects on the endocrine system. Hormones studied include testosterone, luteinizing hormone (LH), follicle stimulating hormone (FSH), sex hormone binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEA-S), prolactin, cortisol, estradiol, insulin, aldosterone, parathormone, glucagon, thyroid stimulating hormone (TSH), triiodothyronine (T3), thyroxine (T4), and somatotrophic hormone (STH). Lansoprazole in oral doses of 15 to 60 mg for up to one year had no clinically significant effect on sexual function. In addition, lansoprazole in oral doses of 15 to 60 mg for two to eight weeks had no clinically significant effect on thyroid function. In 24-month carcinogenicity studies in Sprague-Dawley rats with daily lansoprazole dosages up to 150 mg/kg, proliferative changes in the Leydig cells of the testes, including benign neoplasm, were increased compared to control rats.

Other Effects

No systemic effects of lansoprazole on the central nervous system, lymphoid, hematopoietic, renal, hepatic, cardiovascular, or respiratory systems have been found in humans. Among 56 patients who had extensive baseline eye evaluations, no visual toxicity was observed after lansoprazole treatment (up to 180 mg/day) for up to 58 months. After lifetime lansoprazole exposure in rats, focal pancreatic atrophy, diffuse lymphoid hyperplasia in the thymus, and spontaneous retinal atrophy were seen.

Microbiology

Lansoprazole, clarithromycin and/or amoxicillin have been shown to be active against most strains of *Helicobacter pylori* *in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section. [See *Indications and Usage* (1.2)]

Helicobacter pylori Pretreatment Resistance

Clarithromycin pretreatment resistance (≥ 2 mcg/mL) was 9.5% (91/960) by E-test and 11.3% (12/106) by agar dilution in the dual and triple therapy clinical trials (M93-125, M93-130, M93-131, M95-392, and M95-399).

Amoxicillin pretreatment susceptible isolates (less than/equal to 0.25 mcg/mL) occurred in 97.8% (936/957) and 98% (98/100) of the patients in the dual and triple therapy clinical trials by E-test and agar dilution, respectively. Twenty-one of 957 patients (2.2%) by E-test and 2 of 100 patients (2%) by agar dilution had amoxicillin pretreatment MICs of greater than 0.25 mcg/mL. One patient on the 14-day triple therapy regimen had an unconfirmed pretreatment amoxicillin minimum inhibitory concentration (MIC) of greater than 256 mcg/mL by E-test and the patient was eradicated of *H. pylori*.

Patients not eradicated of *H. pylori* following lansoprazole/amoxicillin/clarithromycin triple therapy will likely have clarithromycin resistant *H. pylori*. Therefore, for those patients who fail therapy, clarithromycin susceptibility testing should be done when possible. Patients with clarithromycin resistant *H. pylori* should not be treated with lansoprazole/amoxicillin/clarithromycin triple therapy or with regimens which include clarithromycin as the sole antimicrobial agent.

Amoxicillin Susceptibility Test Results and Clinical/Bacteriological Outcomes: In the dual and triple therapy clinical trials, 82.6% (195/236) of the patients that had pretreatment amoxicillin susceptible MICs (≤ 0.25 mcg/mL) were eradicated of *H. pylori*. Of those with pretreatment amoxicillin MICs of greater than 0.25 mcg/mL, three of six had the *H. pylori* eradicated. A total of 30% (21/70) of the patients failed lansoprazole 30 mg three times daily/amoxicillin 1 gm three times daily dual therapy and a total of 12.8% (22/172) of the patients failed the 10- and 14-day triple therapy regimens. Post-treatment susceptibility results were not obtained on 11 of the patients who failed therapy. Nine of the 11 patients with amoxicillin post-treatment MICs that failed the triple therapy regimen also had clarithromycin resistant *H. pylori* isolates.

Susceptibility Test for *Helicobacter pylori*: The reference methodology for susceptibility testing of *H. pylori* is agar dilution MICs.¹

One to three microliters of an inoculum equivalent to a No. 2 McFarland standard (1×10^7 to 1×10^8 CFU/mL for *H. pylori*) are inoculated directly onto freshly prepared antimicrobial-containing Mueller-Hinton agar plates with 5% aged defibrinated sheep blood (≥ 2 weeks old). The agar dilution plates are incubated at 35°C in a microaerobic environment produced by a gas generating system suitable for campylobacters.

12.3 Pharmacokinetics

Lansoprazole delayed-release capsules contain an enteric-coated granule formulation of lansoprazole. Absorption of lansoprazole begins only after the granules leave the stomach. Absorption is rapid, with mean peak plasma levels of lansoprazole occurring after approximately 1.7 hours. After a single-dose administration of 15 mg to 60 mg of oral lansoprazole, the peak plasma concentrations (C_{\max}) of lansoprazole and the area under the plasma concentration curves (AUCs) of lansoprazole were approximately proportional to the administered dose. Lansoprazole does not accumulate and its pharmacokinetics are unaltered by multiple dosing.

Absorption: The absorption of lansoprazole is rapid, with the mean C_{\max} occurring approximately 1.7 hours after oral dosing, and the absolute bioavailability is over 80%. In healthy subjects, the mean (\pm SD) plasma half-life was 1.5 (± 1) hours. Both the C_{\max} and AUC are diminished by about 50% to 70% if lansoprazole is given 30 minutes after food, compared to the fasting condition. There is no significant food effect if lansoprazole is given before meals.

Distribution: Lansoprazole is 97% bound to plasma proteins. Plasma protein binding is constant over the concentration range of 0.05 to 5 mcg/mL.

Metabolism: Lansoprazole is extensively metabolized in the liver. Two metabolites have been identified in measurable quantities in plasma (the hydroxylated sulfinyl and sulfone derivatives of lansoprazole). These metabolites have very little or no antisecretory activity. Lansoprazole is thought to be transformed into two active species which inhibit acid secretion by blocking the proton pump [$(\text{H}^+, \text{K}^+)\text{-ATPase}$ enzyme system] at the secretory surface of the gastric parietal cell. The two active species are not present in the systemic circulation. The plasma elimination half-life of lansoprazole is less than 2 hours while the acid inhibitory effect lasts more than 24 hours. Therefore, the plasma elimination half-life of lansoprazole does not reflect its duration of suppression of gastric acid secretion.

Elimination: Following single-dose oral administration of lansoprazole, virtually no unchanged lansoprazole was excreted in the urine. In one study, after a single oral dose of ^{14}C -lansoprazole, approximately one-third of the administered radiation was excreted in the urine and two-thirds was recovered in the feces. This implies a significant biliary excretion of the lansoprazole metabolites.

12.4 Specific Populations

Pediatric Use:

One to 17 years of age

The pharmacokinetics of lansoprazole were studied in pediatric patients with GERD aged 1 to 11 years and 12 to 17 years in two separate clinical studies. In children aged 1 to 11 years, lansoprazole was dosed 15 mg daily for subjects weighing ≤ 30 kg and 30 mg daily for subjects weighing greater than 30 kg. Mean C_{max} and AUC values observed on Day 5 of dosing were similar between the two dose groups and were not affected by weight or age within each weight-adjusted dose group used in the study. In adolescent subjects aged 12 to 17 years, subjects were randomized to receive lansoprazole at 15 mg or 30 mg daily. Mean C_{max} and AUC values of lansoprazole were not affected by body weight or age; and nearly dose-proportional increases in mean C_{max} and AUC values were observed between the two dose groups in the study. Overall, lansoprazole pharmacokinetics in pediatric patients aged 1 to 17 years were similar to those observed in healthy adult subjects.

Neonate to less than one year of age

Refer to Section 8.4 for the pharmacokinetics of lansoprazole in pediatric patients with GERD aged less than 28 days and 1 to 11 months.

Geriatric Use: The clearance of lansoprazole is decreased in the elderly, with elimination half-life increased approximately 50% to 100%. Because the mean half-life in the elderly remains between 1.9 to 2.9 hours, repeated once daily dosing does not result in accumulation of lansoprazole. Peak plasma levels were not increased in the elderly. No dosage adjustment is necessary in the elderly [See Use in Specific Populations (8.5)].

Renal Impairment: In patients with severe renal impairment, plasma protein binding decreased by 1% to 1.5% after administration of 60 mg of lansoprazole. Patients with renal impairment had a shortened elimination half-life and decreased total AUC (free and bound). The AUC for free lansoprazole in plasma, however, was not related to the degree of renal impairment; and the C_{max} and t_{max} (time to reach the maximum concentration) were not different than the C_{max} and t_{max} from subjects with normal renal function. No dosage adjustment is necessary in patients with renal impairment [See Use in Specific Populations (8.6)].

Hepatic Impairment: In patients with various degrees of chronic hepatic impairment, the mean plasma half-life of lansoprazole was prolonged from 1.5 hours to 3.2 to 7.2 hours. An increase in the mean AUC of up to 500% was observed at steady state in hepatically-impaired patients compared to healthy subjects. Consider dose reduction in patients with severe hepatic impairment [See Use in Specific Populations (8.7)].

Gender: In a study comparing 12 male and 6 female human subjects who received lansoprazole, no gender differences were found in pharmacokinetics and intragastric pH results [See Use in Specific Populations (8.5)].

12.5 Drug-Drug Interactions

It is theoretically possible that lansoprazole may interfere with the absorption of other drugs where gastric pH is an important determinant of bioavailability (e.g., ketoconazole, ampicillin esters, iron salts, digoxin).

Lansoprazole is metabolized through the cytochrome P_{450} system, specifically through the CYP3A and CYP2C19 isozymes. Studies have shown that lansoprazole does not have clinically significant interactions with other drugs metabolized by the cytochrome P_{450} system, such as warfarin, antipyrine, indomethacin, ibuprofen, phenytoin, propranolol, prednisone, diazepam, or clarithromycin in healthy subjects. These compounds are metabolized through various cytochrome P_{450} isozymes including CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A.

Atazanavir: lansoprazole causes long-lasting inhibition of gastric acid secretion. Lansoprazole substantially decreases the systemic concentrations of the HIV protease inhibitor atazanavir, which is dependent upon the presence of gastric acid for absorption, and may result in a loss of therapeutic effect of atazanavir and the development of HIV resistance. Therefore, lansoprazole, or other proton pump inhibitors, should not be co-administered with atazanavir.

Theophylline: When lansoprazole was administered concomitantly with theophylline (CYP1A2, CYP3A), a minor increase (10%) in the clearance of theophylline was seen. Because of the small magnitude and the direction of the effect on theophylline clearance, this interaction is unlikely to be of clinical concern. Nonetheless, individual patients may require additional titration of their theophylline dosage when lansoprazole is started or stopped to ensure clinically effective blood levels.

Warfarin: In a study of healthy subjects neither the pharmacokinetics of warfarin enantiomers nor prothrombin time were affected following single or multiple 60 mg doses of lansoprazole. However, there have been reports of increased International Normalized Ratio (INR) and prothrombin time in patients receiving proton pump inhibitors, including lansoprazole, and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with proton pump inhibitors and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time.

Methotrexate and 7-hydromethotrexate: In an open-label, single-arm, eight-day, pharmacokinetic study of 28 adult rheumatoid arthritis patients (who required the chronic use of 7.5 to 15 mg of methotrexate given weekly), administration of 7 days of naproxen 500 mg twice daily and lansoprazole 30 mg daily had no effect on the pharmacokinetics of methotrexate and 7-hydroxymethotrexate. While this study was not designed to assess the safety of this combination of drugs, no major adverse reactions were noted.

Amoxicillin: Lansoprazole has also been shown to have no clinically significant interaction with amoxicillin.

Sucralfate: In a single-dose crossover study examining lansoprazole 30 mg and omeprazole 20 mg each administered alone and concomitantly with sucralfate 1 gram, absorption of the proton pump inhibitors was delayed and their bioavailability was reduced by 17% and 16%, respectively, when administered concomitantly with sucralfate. Therefore, proton pump inhibitors should be taken at least 30 minutes prior to sucralfate. In clinical trials, antacids were administered concomitantly with lansoprazole and there was no evidence of a change in the efficacy of lansoprazole.

13 NONCLINICAL TOXICOLOGY13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In two 24-month carcinogenicity studies, Sprague-Dawley rats were treated with oral lansoprazole doses of 5 to 150 mg/kg/day, about 1 to 40 times the exposure on a body surface (mg/m²) basis of a 50 kg person of average height (1.46 m² BSA) given the recommended human dose of lansoprazole (30 mg/day). Lansoprazole produced dose-related gastric enterochromaffin-like (ECL) cell hyperplasia and ECL cell carcinoids in both male and female rats. It also increased the incidence of intestinal metaplasia of the gastric epithelium in both sexes. In male rats, lansoprazole produced a dose-related increase of testicular interstitial cell adenomas. The incidence of these adenomas in rats receiving doses of 15 to 150 mg/kg/day (4 to 40 times the recommended human dose based on BSA) exceeded the low background incidence (range = 1.4 to 10%) for this strain of rat. In addition, in a one-year toxicity study, testicular interstitial cell adenoma occurred in 1 of 30 rats treated with 50 mg/kg/day of lansoprazole (13 times the recommended human dose based on BSA).

In a 24-month carcinogenicity study, CD-1 mice were treated with oral lansoprazole doses of 15 to 600 mg/kg/day, 2 to 80 times the recommended human dose based on BSA. Lansoprazole produced a dose-related increased incidence of gastric ECL cell hyperplasia. It also produced an increased incidence of liver tumors (hepatocellular adenoma plus carcinoma). The tumor incidences in male mice treated with 300 and 600 mg/kg/day (40 to 80 times the recommended human dose based on BSA) and female mice treated with 150 to 600 mg/kg/day (20 to 80 times the recommended human dose based on BSA) exceeded the ranges of background incidences in historical controls for this strain of mice. Lansoprazole treatment produced adenoma of rete testis in male mice receiving 75 to 600 mg/kg/day (10 to 80 times the recommended human dose based on BSA).

A 26-week p53 (+/-) transgenic mouse carcinogenicity study was not positive.

Lansoprazole was not genotoxic in the Ames test, the *ex vivo* rat hepatocyte unscheduled DNA synthesis (UDS) test, the *in vivo* mouse micronucleus test, or the rat bone marrow cell chromosomal aberration test. It was positive in *in vitro* human lymphocyte chromosomal aberration assays.

Lansoprazole at oral doses up to 150 mg/kg/day (40 times the recommended human dose based on BSA) was found to have no effect on fertility and reproductive performance of male and female rats.

In a U.S. multicenter, double-blind, placebo-controlled, dose-response (15, 30, and 60 mg of lansoprazole once daily) study of 284 patients with endoscopically documented duodenal ulcer, the percentage of patients healed after two and four weeks was significantly higher with all doses of lansoprazole than with placebo. There was no evidence of a greater or earlier response with the two higher doses compared with lansoprazole 15 mg. Based on this study and the second study described below, the recommended dose of lansoprazole in duodenal ulcer is 15 mg per day.

Lansoprazole 15 mg was significantly more effective than placebo in relieving day and nighttime abdominal pain and in decreasing the amount of antacid taken per day.

In a second U.S. multicenter study, also double-blind, placebo-controlled, dose-comparison (15 and 30 mg of lansoprazole once daily), and including a comparison with ranitidine, in 280 patients with endoscopically documented duodenal ulcer, the percentage of patients healed after four weeks was significantly higher with both doses of lansoprazole than with placebo. There was no evidence of a greater or earlier response with the higher dose of lansoprazole. Although the 15 mg dose of lansoprazole was superior to ranitidine at 4 weeks, the lack of significant difference at 2 weeks and the absence of a difference between 30 mg of lansoprazole and ranitidine leaves the comparative effectiveness of the two agents undetermined.

***H. pylori* Eradication to Reduce the Risk of Duodenal Ulcer Recurrence**

Randomized, double-blind clinical studies performed in the U.S. in patients with *H. pylori* and duodenal ulcer disease (defined as an active ulcer or history of an ulcer within one year) evaluated the efficacy of lansoprazole in combination with amoxicillin capsules and clarithromycin tablets as triple 14-day therapy or in combination with amoxicillin capsules as dual 14-day therapy for the eradication of *H. pylori*. Based on the results of these studies, the safety and efficacy of two different eradication regimens were established:

- | | |
|-----------------|--|
| Triple therapy: | Lansoprazole 30 mg twice daily/amoxicillin 1 g twice daily/clarithromycin 500 mg twice daily |
| Dual therapy: | Lansoprazole 30 mg three times daily/amoxicillin 1 g three times daily |

All treatments were for 14 days. *H. pylori* eradication was defined as two negative tests (culture and histology) at 4 to 6 weeks following the end of treatment.

Triple therapy was shown to be more effective than all possible dual therapy combinations. Dual therapy was shown to be more effective than both monotherapies. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence.

A randomized, double-blind clinical study performed in the U.S. in patients with *H. pylori* and duodenal ulcer disease (defined as an active ulcer or history of an ulcer within one year) compared the efficacy of lansoprazole triple therapy for 10 and 14 days. This study established that the 10-day triple therapy was equivalent to the 14-day triple therapy in eradicating *H. pylori*.

Long-Term Maintenance Treatment of Duodenal Ulcers

Lansoprazole has been shown to prevent the recurrence of duodenal ulcers. Two independent, double-blind, multicenter, controlled trials were conducted in patients with endoscopically confirmed healed duodenal ulcers. Patients remained healed significantly longer and the number of recurrences of duodenal ulcers was significantly less in patients treated with lansoprazole than in patients treated with placebo over a 12-month period.

Patients treated with any lansoprazole dose reported significantly less day and night abdominal pain along with fewer days of antacid use and fewer antacid tablets used per day than the placebo group.

Independent substantiation of the effectiveness of lansoprazole 30 mg was provided by a meta-analysis of published and unpublished data.

Healing of NSAID-Associated Gastric Ulcer

In two U.S. and Canadian multicenter, double-blind, active-controlled studies in patients with endoscopically confirmed NSAID-associated gastric ulcer who continued their NSAID use, the percentage of patients healed after 8 weeks was statistically significantly higher with 30 mg of lansoprazole than with the active control. A total of 711 patients were enrolled in the study, and 701 patients were treated. Patients ranged in age from 18 to 88 years (median age 59 years), with 67% female patients and 33% male patients. Race was distributed as follows: 87% Caucasian, 8% Black, 5% Other. There was no statistically significant difference between lansoprazole 30 mg daily and the active control on symptom relief (i.e., abdominal pain).

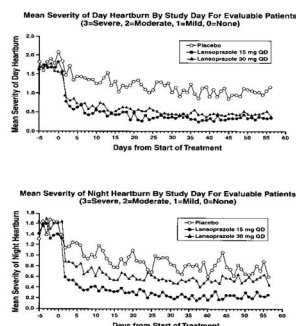
Risk Reduction of NSAID-Associated Gastric Ulcer

In one large U.S., multicenter, double-blind, placebo- and misoprostol-controlled (misoprostol blinded only to the endoscopist) study in patients who required chronic use of an NSAID and who had a history of an endoscopically documented gastric ulcer, the proportion of patients remaining free from gastric ulcer at 4, 8, and 12 weeks was significantly higher with 15 or 30 mg of lansoprazole than placebo. A total of 537 patients were enrolled in the study, and 535 patients were treated. Patients ranged in age from 23 to 89 years (median age 60 years), with 65% female patients and 35% male patients. Race was distributed as follows: 90% Caucasian, 6% Black, 4% other. The 30 mg dose of lansoprazole demonstrated no additional benefit in risk reduction of the NSAID-associated gastric ulcer than the 15 mg dose.

Gastroesophageal Reflux Disease (GERD)

Symptomatic GERD: In a U.S. multicenter, double-blind, placebo-controlled study of 214 patients with frequent GERD symptoms, but no esophageal erosions by endoscopy, significantly greater relief of heartburn associated with GERD was observed with the administration of lansoprazole 15 mg once daily up to 8 weeks than with placebo. No significant additional benefit from lansoprazole 30 mg once daily was observed.

The intent-to-treat analyses demonstrated significant reduction in frequency and severity of day and night heartburn. Data for frequency and severity for the 8-week treatment period are presented in Figures 1 and 2:



In two U.S., multicenter double-blind, ranitidine-controlled studies of 925 total patients with frequent GERD symptoms, but no esophageal erosions by endoscopy, lansoprazole 15 mg was superior to ranitidine 150 mg (twice daily) in decreasing the frequency and severity of day and night heartburn associated with GERD for the 8-week treatment period. No significant additional benefit from lansoprazole 30 mg once daily was observed. [See *Indications and Usage* (1.7)]

In this study, all lansoprazole groups reported significantly greater relief of heartburn and less day and night abdominal pain along with fewer days of antacid use and fewer antacid tablets taken per day than the placebo group.

Although all doses were effective, the earlier healing in the higher two doses suggests 30 mg daily as the recommended dose.

Lansoprazole was also compared in a U.S. multicenter, double-blind study to a low dose of ranitidine in 242 patients with erosive reflux esophagitis. Lansoprazole at a dose of 30 mg was significantly more effective than ranitidine 150 mg twice daily.

In addition, patients treated with lansoprazole reported less day and nighttime heartburn and took less antacid tablets for fewer days than patients taking ranitidine 150 mg twice daily.

Although this study demonstrates effectiveness of lansoprazole in healing erosive esophagitis, it does not represent an adequate comparison with ranitidine because the recommended ranitidine dose for esophagitis is 150 mg q.i.d., twice the dose used in this study.

In the two trials described and in several smaller studies involving patients with moderate to severe erosive esophagitis, lansoprazole produced healing rates similar to those shown above.

In a U.S. multicenter, double-blind, active-controlled study, 30 mg of lansoprazole was compared with ranitidine 150 mg twice daily in 151 patients with erosive reflux esophagitis that was poorly responsive to a minimum of 12 weeks of treatment with at least one H₂-receptor antagonist given at the dose indicated for symptom relief or greater, namely, cimetidine 800 mg/day, ranitidine 300 mg/day, famotidine 40 mg/day or nizatidine 300 mg/day. Lansoprazole 30 mg was more effective than ranitidine 150 mg twice daily in healing reflux esophagitis, and the percentage of patients with healing were as follows. This study does not constitute a comparison of the effectiveness of histamine H₂-receptor antagonists with lansoprazole, as all patients had demonstrated unresponsiveness to the histamine H₂-receptor antagonist mode of treatment. It does indicate, however, that lansoprazole may be useful in patients failing on a histamine H₂-receptor antagonist.

Long-Term Maintenance Treatment of Erosive Esophagitis

Two independent, double-blind, multicenter, controlled trials were conducted in patients with endoscopically confirmed healed esophagitis. Patients remained in remission significantly longer and the number of recurrences of erosive esophagitis was significantly less in patients treated with lansoprazole than in patients treated with placebo over a 12-month period.

Regardless of initial grade of erosive esophagitis, lansoprazole 15 mg and 30 mg were similar in maintaining remission.

In a U.S., randomized, double-blind, study, lansoprazole 15 mg daily (n = 100) was compared with ranitidine 150 mg twice daily (n = 106), at the recommended dosage, in patients with endoscopically-proven healed erosive esophagitis over a 12-month period. Treatment with lansoprazole resulted in patients remaining healed (Grade 0 lesions) of erosive esophagitis for significantly longer periods of time than those treated with ranitidine (p less than 0.001). In addition, lansoprazole was significantly more effective than ranitidine in providing complete relief of both daytime and nighttime heartburn. Patients treated with lansoprazole remained asymptomatic for a significantly longer period of time than patients treated with ranitidine. [See *Indications and Usage* (1.8)]

Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome

In open studies of 57 patients with pathological hypersecretory conditions, such as Zollinger-Ellison syndrome (ZES) with or without multiple endocrine adenomas, lansoprazole significantly inhibited gastric acid secretion and controlled associated symptoms of diarrhea, anorexia and pain. Doses ranging from 15 mg every other day to 180 mg per day maintained basal acid secretion below 10 mEq/hr in patients without prior gastric surgery and below 5 mEq/hr in patients with prior gastric surgery.

Initial doses were titrated to the individual patient need, and adjustments were necessary with time in some patients. [See *Dosage and Administration* (2.1)] Lansoprazole was well tolerated at these high dose levels for prolonged periods (greater than four years in some patients). In most ZES patients, serum gastrin levels were not modified by lansoprazole. However, in some patients, serum gastrin increased to levels greater than those present prior to initiation of lansoprazole therapy. [See *Indications and Usage* (1.9)]

15 REFERENCES

1. National Committee for Clinical Laboratory Standards. Summary Minutes, Subcommittee on Antimicrobial Susceptibility Testing, Tampa, FL, January 11-13, 1998.

1 INDICATIONS AND USAGE

1.1 Short-Term Treatment of Active Duodenal Ulcer

Lansoprazole delayed-release capsules are indicated for short-term treatment (for 4 weeks) for healing and symptom relief of active duodenal ulcer. [See *Clinical Studies* (14)]

1.2 *H. pylori* Eradication to Reduce the Risk of Duodenal Ulcer Recurrence

Triple Therapy: lansoprazole/amoxicillin/clarithromycin

Lansoprazole delayed-release capsules in combination with amoxicillin plus clarithromycin as triple therapy are indicated for the treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or one-year history of a duodenal ulcer) to eradicate *H. pylori*. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence. [See *Clinical Studies* (14)]

Please refer to the full prescribing information for amoxicillin and clarithromycin.

Dual Therapy: lansoprazole/amoxicillin

Lansoprazole delayed-release capsules in combination with amoxicillin as dual therapy are indicated for the treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or one-year history of a duodenal ulcer) **who are either allergic or intolerant to clarithromycin or in whom resistance to clarithromycin is known or suspected** (see the clarithromycin package insert, MICROBIOLOGY section). Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence. [See *Clinical Studies* (14)]

Please refer to the full prescribing information for amoxicillin.

1.3 Maintenance of Healed Duodenal Ulcers

Lansoprazole delayed-release capsules are indicated to maintain healing of duodenal ulcers. Controlled studies do not extend beyond 12 months. [See *Clinical Studies* (14)]

1.4 Short-Term Treatment of Active Benign Gastric Ulcer

Lansoprazole delayed-release capsules are indicated for short-term treatment (up to 8 weeks) for healing and symptom relief of active benign gastric ulcer. [See *Clinical Studies (14)*]

1.5 Healing of NSAID-Associated Gastric Ulcer

Lansoprazole delayed-release capsules are indicated for the treatment of NSAID-associated gastric ulcer in patients who continue NSAID use. Controlled studies did not extend beyond 8 weeks. [See *Clinical Studies (14)*]

1.6 Risk Reduction of NSAID-Associated Gastric Ulcer

Lansoprazole delayed-release capsules are indicated for reducing the risk of NSAID-associated gastric ulcers in patients with a history of a documented gastric ulcer who require the use of an NSAID. Controlled studies did not extend beyond 12 weeks. [See *Clinical Studies (14)*]

1.7 Gastroesophageal Reflux Disease (GERD)

Short-Term Treatment of Symptomatic GERD

Lansoprazole delayed-release capsules are indicated for the treatment of heartburn and other symptoms associated with GERD. [See *Clinical Studies (14)*]

Short-Term Treatment of Erosive Esophagitis

Lansoprazole delayed-release capsules are indicated for short-term treatment (up to 8 weeks) for healing and symptom relief of all grades of erosive esophagitis. For patients who do not heal with lansoprazole delayed-release capsules for 8 weeks (5 to 10%), it may be helpful to give an additional 8 weeks of treatment. If there is a recurrence of erosive esophagitis an additional 8-week course with lansoprazole delayed-release capsules may be considered. [See *Clinical Studies (14)*]

1.8 Maintenance of Healing of Erosive Esophagitis (EE)

Lansoprazole delayed-release capsules are indicated to maintain healing of erosive esophagitis. Controlled studies did not extend beyond 12 months. [See *Clinical Studies (14)*]

1.9 Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome

Lansoprazole delayed-release capsules are indicated for the long-term treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome. [See *Clinical Studies (14)*]

4 CONTRAINDICATIONS

Lansoprazole is contraindicated in patients with known severe hypersensitivity to any component of the formulation of lansoprazole. For information on contraindications for amoxicillin or clarithromycin, refer to their full prescribing information, CONTRAINDICATIONS sections.

5 WARNINGS AND PRECAUTIONS

Symptomatic response to therapy with lansoprazole does not preclude the presence of gastric malignancy. For information on warnings and precautions for amoxicillin or clarithromycin, refer to their full prescribing information, WARNINGS and PRECAUTIONS sections.

6 ADVERSE REACTIONS

6.1 Clinical

Worldwide, over 10,000 patients have been treated with lansoprazole in Phase 2 or Phase 3 clinical trials involving various dosages and durations of treatment. In general, lansoprazole treatment has been well-tolerated in both short-term and long-term trials.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Headache was also seen at greater than 1% incidence but was more common on placebo. The incidence of diarrhea was similar between patients who received placebo and patients who received 15 mg and 30 mg of lansoprazole, but higher in the patients who received 60 mg of lansoprazole (2.9%, 1.4%, 4.2%, and 7.4%, respectively).

The most commonly reported possibly or probably treatment-related adverse event during maintenance therapy was diarrhea.

In the risk reduction study of lansoprazole for NSAID-associated gastric ulcers, the incidence of diarrhea for patients treated with lansoprazole, misoprostol, and placebo was 5%, 22%, and 3%, respectively.

Another study for the same indication, where patients took either a COX-2 inhibitor or lansoprazole and naproxen, demonstrated that the safety profile was similar to the prior study. Additional reactions from this study not previously observed in other clinical trials with lansoprazole included contusion, duodenitis, epigastric discomfort, esophageal disorder, fatigue, hunger, hiatal hernia, hoarseness, impaired gastric emptying, metaplasia, and renal impairment.

Additional adverse experiences occurring in less than 1% of patients or subjects who received lansoprazole in domestic trials are shown below:

Body as a Whole – abdomen enlarged, allergic reaction, asthenia, back pain, candidiasis, carcinoma, chest pain (not otherwise specified), chills, edema, fever, flu syndrome, halitosis, infection (not otherwise specified), malaise, neck pain, neck rigidity, pain, pelvic pain

Cardiovascular System - angina, arrhythmia, bradycardia, cerebrovascular accident/cerebral infarction, hypertension/hypotension, migraine, myocardial infarction, palpitations, shock (circulatory failure), syncope, tachycardia, vasodilation

Digestive System – abnormal stools, anorexia, bezoar, cardiospasm, cholelithiasis, colitis, dry mouth, dyspepsia, dysphagia, enteritis, eructation, esophageal stenosis, esophageal ulcer, esophagitis, fecal discoloration, flatulence, gastric nodules/fundic gland polyps, gastritis, gastroenteritis, gastrointestinal anomaly, gastrointestinal disorder, gastrointestinal hemorrhage, glossitis, gum hemorrhage, hematemesis, increased appetite, increased salivation, melena, mouth ulceration, nausea and vomiting, nausea and vomiting and diarrhea, gastrointestinal moniliasis, rectal disorder, rectal hemorrhage, stomatitis, tenesmus, thirst, tongue disorder, ulcerative colitis, ulcerative stomatitis

Endocrine System - diabetes mellitus, goiter, hypothyroidism

Hemic and Lymphatic System - anemia, hemolysis, lymphadenopathy

Metabolic and Nutritional Disorders - avitaminosis, gout, dehydration, hyperglycemia/hypoglycemia, peripheral edema, weight gain/loss

Musculoskeletal System - arthralgia, arthritis, bone disorder, joint disorder, leg cramps, musculoskeletal pain, myalgia, myasthenia, ptosis, synovitis

Nervous System – abnormal dreams, agitation, amnesia, anxiety, apathy, confusion, convulsion, dementia, depersonalization, depression, diplopia, dizziness, emotional lability, hallucinations, hemiplegia, hostility aggravated, hyperkinesia, hypertonia, hypesthesia, insomnia, libido decreased/increased, nervousness, neurosis, paresthesia, sleep disorder, somnolence, thinking abnormality, tremor, vertigo

Respiratory System - asthma, bronchitis, cough increased, dyspnea, epistaxis, hemoptysis, hiccup, laryngeal neoplasia, lung fibrosis, pharyngitis, pleural disorder, pneumonia, respiratory disorder, upper respiratory inflammation/infection, rhinitis, sinusitis, stridor

Skin and Appendages - acne, alopecia, contact dermatitis, dry skin, fixed eruption, hair disorder, maculopapular rash, nail disorder, pruritus, rash, skin carcinoma, skin disorder, sweating, urticaria

Special Senses – abnormal vision, amblyopia, blepharitis, blurred vision, cataract, conjunctivitis, deafness, dry eyes, ear/eye disorder, eye pain, glaucoma, otitis media, parosmia, photophobia, retinal degeneration/disorder, taste loss, taste perversion, tinnitus, visual field defect

Urogenital System - abnormal menses, breast enlargement, breast pain, breast tenderness, dysmenorrhea, dysuria, gynecomastia, impotence, kidney calculus, kidney pain, leukorrhea, menorrhagia, menstrual disorder, penis disorder, polyuria, testis disorder, urethral pain, urinary frequency, urinary retention, urinary tract infection, urinary urgency, urination impaired, vaginitis.

6.2 Postmarketing Experience

Additional adverse experiences have been reported since lansoprazole delayed-release capsules have been marketed. The majority of these cases are foreign-sourced and a relationship to lansoprazole delayed-release capsules have not been established. Because these reactions were reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events are listed below by COSTART body system.

Body as a Whole – anaphylactic/anaphylactoid reactions; *Digestive System* - hepatotoxicity, pancreatitis, vomiting; *Hemic and Lymphatic System* - agranulocytosis, aplastic anemia, hemolytic anemia, leukopenia, neutropenia, pancytopenia, thrombocytopenia, and thrombotic thrombocytopenic purpura; *Musculoskeletal System* - myositis; *Skin and Appendages* – severe dermatologic reactions including erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (some fatal); *Special Senses* - speech disorder; *Urogenital System* – interstitial nephritis, urinary retention.

6.3 Combination Therapy with Amoxicillin and Clarithromycin

In clinical trials using combination therapy with lansoprazole plus amoxicillin and clarithromycin, and lansoprazole plus amoxicillin, no adverse reactions peculiar to these drug combinations were observed. Adverse reactions that have occurred have been limited to those that had been previously reported with lansoprazole, amoxicillin, or clarithromycin.

Triple Therapy: lansoprazole/amoxicillin/clarithromycin

The most frequently reported adverse reactions for patients who received triple therapy for 14 days were diarrhea (7%), headache (6%), and taste perversion (5%). There were no statistically significant differences in the frequency of reported adverse reactions between the 10- and 14-day triple therapy regimens. No treatment-emergent adverse reactions were observed at significantly higher rates with triple therapy than with any dual therapy regimen.

Dual Therapy: lansoprazole/amoxicillin

The most frequently reported adverse reactions for patients who received lansoprazole three times daily plus amoxicillin three times daily dual therapy were diarrhea (8%) and headache (7%). No treatment-emergent adverse reactions were observed at significantly higher rates with lansoprazole three times daily plus amoxicillin three times daily dual therapy than with lansoprazole alone.

For information on adverse reactions with amoxicillin or clarithromycin, refer to their full prescribing information, ADVERSE REACTIONS sections.

6.4 Laboratory Values

The following changes in laboratory parameters in patients who received lansoprazole were reported as adverse reactions:

Abnormal liver function tests, increased SGOT (AST), increased SGPT (ALT), increased creatinine, increased alkaline phosphatase, increased globulins, increased GGTP, increased/decreased/abnormal WBC, abnormal AG ratio, abnormal RBC, bilirubinemia, blood potassium increased, blood urea increased, crystal urine present, eosinophilia, hemoglobin decreased, hyperlipemia, increased/decreased electrolytes, increased/decreased cholesterol, increased glucocorticoids, increased LDH, increased/decreased/abnormal platelets, increased gastrin levels and positive fecal occult blood. Urine abnormalities such as albuminuria, glycosuria, and hematuria were also reported. Additional isolated laboratory abnormalities were reported.

In the placebo controlled studies, when SGOT (AST) and SGPT (ALT) were evaluated, 0.4% (4/978) and 0.4% (11/2677) patients, who received placebo and lansoprazole, respectively, had enzyme elevations greater than three times the upper limit of normal range at the final treatment visit. None of these patients who received lansoprazole reported jaundice at any time during the study.

In clinical trials using combination therapy with lansoprazole plus amoxicillin and clarithromycin, and lansoprazole plus amoxicillin, no increased laboratory abnormalities particular to these drug combinations were observed.

For information on laboratory value changes with amoxicillin or clarithromycin, refer to their full prescribing information, ADVERSE REACTIONS sections.

7 DRUG INTERACTIONS

Drugs with pH-Dependent Absorption Kinetics

Lansoprazole causes long-lasting inhibition of gastric acid secretion. Lansoprazole and other PPIs are likely to substantially decrease the systemic concentrations of the HIV protease inhibitor atazanavir, which is dependent upon the presence of gastric acid for absorption, and may result in a loss of therapeutic effect of atazanavir and the development of HIV resistance. Therefore, lansoprazole and other PPIs should not be co-administered with atazanavir. [See *Clinical Pharmacology* (12.5)]

It is theoretically possible that lansoprazole and other PPIs may interfere with the absorption of other drugs where gastric pH is an important determinant of oral bioavailability (e.g., ampicillin esters, digoxin, iron salts, ketoconazole). [See *Clinical Pharmacology* (12.5)]

Warfarin

In a study of healthy subjects, co-administration of single or multiple 60 mg doses of lansoprazole and warfarin did not affect the pharmacokinetics of warfarin nor prothrombin time. [see *Clinical Pharmacology* (12.5)] However, there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with PPIs and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time. [See *Clinical Pharmacology* (12.5)]

Tacrolimus

Concomitant administration of lansoprazole and tacrolimus may increase whole blood levels of tacrolimus, especially in transplant patients who are intermediate or poor metabolizers of CYP2C19.

Theophylline

A minor increase (10%) in the clearance of theophylline was observed following the administration of lansoprazole concomitantly with theophylline. Although the magnitude of the effect on theophylline clearance is small, individual patients may require additional titration of their theophylline dosage when lansoprazole is started or stopped to ensure clinically effective blood levels. [See *Clinical Pharmacology* (12.5)]

For information on drug interactions for amoxicillin or clarithromycin, refer to their full prescribing information, DRUG INTERACTIONS sections.

8 USE IN SPECIFIC POPULATIONS8.1 Pregnancy

Teratogenic effects

Pregnancy Category B. Reproduction studies have been performed in pregnant rats at oral lansoprazole doses up to 150 mg/kg/day [49 times the recommended human dose (30 mg/day) based on body surface area (BSA)] and pregnant rabbits at oral lansoprazole doses up to 30 mg/kg/day (19 times the recommended human dose based on BSA) and have revealed no evidence of impaired fertility or harm to the fetus due to lansoprazole. There are, however, no adequate or well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. See full prescribing information for clarithromycin before using in pregnant women.

8.3 Nursing Mothers

Lansoprazole or its metabolites are excreted in the milk of rats. It is not known whether lansoprazole is excreted in human milk. Because many drugs are excreted in human milk, because of the potential for serious adverse reactions in nursing infants from lansoprazole, and because of the potential for tumorigenicity shown for lansoprazole in rat carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue lansoprazole, taking into account the importance of lansoprazole to the mother.

8.4 Pediatric Use

The safety and effectiveness of lansoprazole have been established in pediatric patients 1 to 17 years of age for short-term treatment of symptomatic GERD and erosive esophagitis, however, lansoprazole was not effective in patients with symptomatic GERD 1 month to less than 1 year of age in a multi-center, double-blind, placebo controlled study

Neonate to less than 1 year of age

The pharmacokinetics of lansoprazole were studied in pediatric patients with GERD aged less than 28 days and 1 to 11 months. Compared to healthy adults receiving 30 mg, neonates had higher exposure (mean weight-based normalized AUC values 2.04- and 1.88-fold higher at doses of 0.5 mg/kg/day and 1 mg/kg/day, respectively). Infants aged less than/equal to 10 weeks had clearance and exposure values that were similar to neonates. Infants aged greater than 10 weeks who received 1 mg/kg/day had mean AUC values that were similar to adults who received a 30 mg dose.

Lansoprazole was not found to be effective in a U.S. and Polish 4 week multicenter, double-blind, placebo-controlled, parallel-group study of 162 patients between one month and less than 12 months of age with symptomatic GERD based on a medical history of crying/fussing/irritability associated with feedings who had not responded to conservative GERD management (i.e., non-pharmacologic intervention) for 7 to 14 days. Patients received lansoprazole as a suspension daily (0.2 to 0.3 mg/kg/day in infants less than/equal to 10 weeks of age or 1 to 1.5 mg/kg/day in infants greater than 10 weeks or placebo) for up to 4 weeks of double-blind treatment.

The primary efficacy endpoint was assessed by greater than 50% reduction from baseline in either the percent of feedings with a crying/fussing/irritability episode or the duration (minutes) of a crying/fussing/irritability episode within one hour after feeding. There was no difference in the percentage of responders between the lansoprazole pediatric suspension group and placebo group (54% in both groups).

There were no adverse events reported in pediatric clinical studies (1 month to less than 12 months of age) that were not previously observed in adults.

Based on the results of the Phase 3 efficacy study, lansoprazole was not shown to be effective. Therefore, these results do not support the use of lansoprazole in treating symptomatic GERD in infants.

One to 11 years of age

In an uncontrolled, open-label, U.S. multicenter study, 66 pediatric patients (1 to 11 years of age) with GERD were assigned, based on body weight, to receive an initial dose of either lansoprazole 15 mg daily if less than/equal to 30 kg or lansoprazole 30 mg daily if greater than 30 kg administered for 8 to 12 weeks. The lansoprazole dose was increased (up to 30 mg twice daily) in 24 of 66 pediatric patients after 2 or more weeks of treatment if they remained symptomatic. At baseline 85% of patients had mild to moderate overall GERD symptoms (assessed by investigator interview), 58% had non-erosive GERD and 42% had erosive esophagitis (assessed by endoscopy).

After 8 to 12 weeks of lansoprazole treatment, the intent-to-treat analysis demonstrated an approximate 50% reduction in frequency and severity of GERD symptoms.

Twenty-one of 27 erosive esophagitis patients were healed at 8 weeks and 100% of patients were healed at 12 weeks by endoscopy. In a study of 66 pediatric patients in the age group 1 year to 11 years old after treatment with lansoprazole given orally in doses of 15 mg daily to 30 mg twice daily, increases in serum gastrin levels were similar to those observed in adult studies. Median fasting serum gastrin levels increased 89% from 51 pg/mL at baseline to 97 pg/mL [interquartile range (25th to 75th percentile) of 71 to 130 pg/mL] at the final visit.

The pediatric safety of lansoprazole delayed-release capsules has been assessed in 66 pediatric patients aged 1 to 11 years of age. Of the 66 patients with GERD 85% (56/66) took lansoprazole for 8 weeks and 15% (10/66) took it for 12 weeks.

The most frequently reported (2 or more patients) treatment-related adverse reactions in patients 1 to 11 years of age (N=66) were constipation (5%) and headache (3%).

Twelve to 17 years of age

In an uncontrolled, open-label, U.S. multicenter study, 87 adolescent patients (12 to 17 years of age) with symptomatic GERD were treated with lansoprazole for 8 to 12 weeks. Baseline upper endoscopies classified these patients into two groups: 64 (74%) nonerosive GERD and 23 (26%) erosive esophagitis (EE). The nonerosive GERD patients received lansoprazole 15 mg daily for 8 weeks and the EE patients received lansoprazole 30 mg daily for 8 to 12 weeks. At baseline, 89% of these patients had mild to moderate overall GERD symptoms (assessed by investigator interviews). During 8 weeks of lansoprazole treatment, adolescent patients experienced a 63% reduction in frequency and a 69% reduction in severity of GERD symptoms based on diary results.

Twenty-one of 22 (95.5%) adolescent erosive esophagitis patients were healed after 8 weeks of lansoprazole treatment. One patient remained unhealed after 12 weeks of treatment (Table 3).

In these 87 adolescent patients, increases in serum gastrin levels were similar to those observed in adult studies, median fasting serum gastrin levels increased 42% from 45 pg/mL at baseline to 64 pg/mL [interquartile range (25th to 75th percentile) of 44 to 88 pg/mL] at the final visit. (Normal serum gastrin levels are 25 to 111 pg/mL).

The safety of lansoprazole delayed-release capsules has been assessed in these 87 adolescent patients. Of the 87 adolescent patients with GERD, 6% (5/87) took lansoprazole for less than 6 weeks, 93% (81/87) for 6 to 10 weeks, and 1% (1/87) for greater than 10 weeks.

The most frequently reported (at least 3%) treatment-related adverse reactions in these patients were headache (7%), abdominal pain (5%), nausea (3%) and dizziness (3%). Treatment-related dizziness, reported in this package insert as occurring in less than 1% of adult patients, was reported in this study by 3 adolescent patients with nonerosive GERD, who had dizziness concurrently with other reactions (such as migraine, dyspnea, and vomiting).

8.5 Geriatric Use

No dosage adjustment of lansoprazole is necessary in geriatric patients. The incidence rates of lansoprazole-associated adverse reactions and laboratory test abnormalities are similar to those seen in younger patients. [See *Clinical Pharmacology* (12.4)]

8.6 Renal Impairment

No dosage adjustment of lansoprazole is necessary in patients with renal impairment. The pharmacokinetics of lansoprazole in patients with various degrees of renal impairment were not substantially different compared to those in subjects with normal renal function.

[See *Clinical Pharmacology* (12.4)]

8.7 Hepatic Impairment

In patients with various degrees of chronic hepatic impairment, an increase in the mean AUC of up to 500% was observed at steady state compared to healthy subjects. Consider dose reduction in patients with severe hepatic impairment. [See *Clinical Pharmacology* (12.4)]

8.8 Gender

Over 4,000 women were treated with lansoprazole. Ulcer healing rates in females were similar to those in males. The incidence rates of adverse reactions in females were similar to those seen in males. [See *Clinical Pharmacology* (12.4)]

8.9 Race

The pooled mean pharmacokinetic parameters of lansoprazole from twelve U.S. Phase 1 studies (N=513) were compared to the mean pharmacokinetic parameters from two Asian studies (N=20). The mean AUCs of lansoprazole in Asian subjects were approximately twice those seen in pooled U.S. data; however, the inter-individual variability was high. The C_{max} values were comparable.

10 OVERDOSAGE

Lansoprazole is not removed from the circulation by hemodialysis. In one reported overdose, a patient consumed 600 mg of lansoprazole with no adverse reaction. Oral lansoprazole doses up to 5000 mg/kg in rats (approximately 1600 times the 30 mg human dose based on BSA) and in mice (about 800 times the 30 mg human dose based on BSA) did not produce deaths or any clinical signs.

2 DOSAGE AND ADMINISTRATION

Lansoprazole delayed-release capsules are available in 15 mg and 30 mg strengths. Directions for use specific to the route and available methods of administration is presented below. Lansoprazole delayed-release capsules should be taken before eating. Lansoprazole delayed-release capsules **SHOULD NOT BE CRUSHED OR CHEWED**. In the clinical trials, antacids were used concomitantly with lansoprazole delayed-release capsules.

2.2 Special Populations

Renal impairment patients and geriatric patients do not require dosage adjustment. However, consider dose adjustment in patients with severe liver impairment. [See *Use in Specific Populations* (8.5, 8.6 and 8.7)]

2.3 Important Administration Information

Administration Options

Lansoprazole Delayed-Release Capsules - Oral Administration

- Lansoprazole delayed-release capsules should be swallowed whole.
- Alternatively, for patients who have difficulty swallowing capsules, lansoprazole delayed-release capsules can be opened and administered as follows:
 - Open capsule.
 - Sprinkle intact granules on one tablespoon of either applesauce, ENSURE[®] pudding, cottage cheese, yogurt or strained pears.
 - Swallow immediately.
- Lansoprazole delayed-release capsules may also be emptied into a small volume of either apple juice, orange juice or tomato juice and administered as follows:
 - Open capsule.
 - Sprinkle intact granules into a small volume of either apple juice, orange juice or tomato juice (60 mL – approximately 2 ounces).
 - Mix briefly.
 - Swallow immediately.
 - To ensure complete delivery of the dose, the glass should be rinsed with two or more volumes of juice and the contents swallowed immediately.

USE IN OTHER FOODS AND LIQUIDS HAS NOT BEEN STUDIED CLINICALLY AND IS THEREFORE NOT RECOMMENDED.

Lansoprazole Delayed-Release Capsules - Nasogastric Tube Administration

- For patients who have a nasogastric tube in place, lansoprazole delayed-release capsules can be administered as follows:
 - Open capsule.
 - Mix intact granules into 40 mL of apple juice. **DO NOT USE OTHER LIQUIDS.**
 - Inject through the nasogastric tube into the stomach.
 - Flush with additional apple juice to clear the tube.

3 DOSAGE FORMS AND STRENGTHS

- 15 mg capsules are opaque, hard gelatin, colored pink and green with the TAP logo and "PREVACID 15" imprinted on the capsule.
- 30 mg capsules are opaque, hard gelatin, colored pink and black with the TAP logo and "PREVACID 30" imprinted on the capsule.

16 HOW SUPPLIED/STORAGE AND HANDLING

Lansoprazole Delayed-Release Capsules, 15 mg, are opaque, hard gelatin, colored pink and green with "TAP" and "PREVACID 15" imprinted on the capsules. The 30 mg capsules are opaque, hard gelatin, colored pink and black with "TAP" and "PREVACID 30" imprinted on the capsules. They are available as follows:

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Patient should be informed of the following:

17.1 Information for Patients

Lansoprazole delayed-release capsules are available in 15 mg and 30 mg strengths. Directions for use specific to the route and available methods of administration is presented below. [See *Dosage and Administration* (2.3)]

- Lansoprazole delayed-release capsules should be taken before eating.
- Lansoprazole delayed-release capsules **SHOULD NOT BE CRUSHED OR CHEWED**.

Administration Options

Lansoprazole Delayed-Release Capsules

- Lansoprazole delayed-release capsules should be swallowed whole.
- Alternatively, for patients who have difficulty swallowing capsules, lansoprazole delayed-release capsules can be opened and administered as follows:
 - Open capsule.
 - Sprinkle intact granules on one tablespoon of either applesauce, ENSURE[®] pudding, cottage cheese, yogurt or strained pears.
 - Swallow immediately.
- Lansoprazole delayed-release capsules may also be emptied into a small volume of either apple juice, orange juice or tomato juice and administered as follows:
 - Open capsule.
 - Sprinkle intact granules into a small volume of either apple juice, orange juice or tomato juice (60 mL – approximately 2 ounces).
 - Mix briefly.
 - Swallow immediately.
 - To ensure complete delivery of the dose, the glass should be rinsed with two or more volumes of juice and the contents swallowed immediately.

USE IN OTHER FOODS AND LIQUIDS HAS NOT BEEN STUDIED CLINICALLY AND IS THEREFORE NOT RECOMMENDED.

Manufactured by:

Takeda Ireland Ltd.

Kilruddery, Co. Wicklow, Ireland

for:

Sandoz Inc.

Princeton, NJ 08540

All trademark names are the property of their respective owners.

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Lansoprazole Label

Packaged and distributed by:  **STAT USA** Gainesville, GA 30501

Lansoprazole D/R
30mg 30 Caps

Generic For: **Prevacid**

NDC 16590-891-30 Prod# 891-30 Lot# SAMPLE

Each Capsule Contains: **Lansoprazole 30mg Delayed-Release**

Mfg By: Sandoz Inc.
Princeton, NJ 08540 NDC 0781-2355-01

Mfg Lot: 819392E21
Discard After: 06/12 MD 11/30/2009 9632180

RX ONLY-KEEP OUT OF REACH OF CHILDREN

AMHTF

Caution: Federal law prohibits transfer of this drug to any person other than the patient for whom it was prescribed.



16590-891-30

Dosage: See package insert
Store between 59-86 degrees F